REMARKS

Claims 1-14 and 21 are pending in the application. Claims 1-9, 11, and 13 stand rejected under 35 U.S.C. § 112, first paragraph. Claims 2-9 and 13-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claim 21 is rejected under 35 U.S.C. § 102(b) as being anticipated by Vallee et al., U.S. Patent No. 4,916,073. Claims 1-9, 11, and 13 stand rejected under 35 U.S.C. § 103(a), as being obvious over Vallee et al., U.S. Patent No. 4,916,073, in view of Olson et al., *Cancer Research* (1994) 54:4576, Milligan et al., *J. Med. Chem.* (1993) 36:1923, Burch, U.S. Patent No. 5,135,917, Anderson et al., U.S. Patent No. 5,442,049, and Artavanis-Tsakonas et al., U.S. Patent No. 5,637,471. Applicants gratefully acknowledge that claims 10 and 12 would be allowable if written in independent form including all of the limitations of the base claim and any intervening claim.

Applicants have amended the claims under consideration to more clearly define and distinctly characterize Applicants' novel invention. Support for the amendments to claim 2 can be found in the specification at least at page 4, lines 16-19. Support for the amendments to claim 3 can be found in the specification at least at page 22, lines 5-17. Support for the amendments to claim 4 can be found in the specification at least at page 22, line 5-17 to page 23, line 8. Support for new claim 22 can be found in claim 5 as originally filed. Support for new claims 23 and 24 cane be found in claims 8 and 13 as originally filed. The amendments presented herein contain no new matter. Attached hereto is a marked-up version of the changes made to the claims captioned "Version of Amendments With Markings To Show Changes Made."

Applicants acknowledge the Examiner's request to make specific reference to the earlier filed application. In response, Applicants have amended the specification to recite the patent number and issue date of the earlier filed application.

Applicants are submitting to the Official Draftsperson on even date herewith substitute formal drawing sheets for Figures 1-3. The formal drawing sheets correct the informalities that were present in the previously submitted formal drawings. Applicants respectfully request substitution and approval of the submitted figures.

Applicants respectfully request entry and consideration of the foregoing remarks, which are intended to place this case in condition for allowance.

I. The Specification Provides Adequate Written Description for Claims 1-9, 11, and 13

At page 2, paragraph 3 of the instant Office Action, claims 1-9, 11, and 13 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to those skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner asserts that, while the specification discloses human angiogenin, 8 oligonucleotides targeting the AUG initiation codon and transcriptional start site regions, the 3' termination site, and the 5' TATA box site, no other nucleic acid oligonucleotides that inhibit angiogenin are taught by the specification. The Examiner also asserts that the specification as filed fails to provide any written description at all for other antisense oligonucleotides other than those listed above, or what sequences or molecular structures, other than a generalization that selection of a target site anywhere along the known nucleic acid sequence of the angiogenin gene, is required to make and use antisense oligonucleotides that inhibit the expression of any angiogenin in the invention as claimed.

Applicants respectfully traverse this rejection. Applicants note that the Examiner's rejection is directed to the claims as originally filed with the application. The originally-filed

claims, therefore, are part of the specification as filed. In addition, support for the claims can be found throughout the specification as filed.

Support for claim 1 can be found in the specification at page 8, lines 13-19, where Applicants teach oligonucleotide reagents capable of targeting nucleic acid sequences encoding human angiogenin in a manner to inhibit (i.e., reduce, eliminate, or otherwise interfere with) the expression of angiogenin. Each oligonucleotide, or analog thereof, has a nucleotide or base sequence which is complimentary, i.e., capable of hybridizing with or binding to, at least a portion of the nucleic acid encoding angiogenin, i.e., the angiogenin gene DNA or RNA, which has significance in expressing angiogenin.

Support for claim 2 can be found in the specification at page 8, line 19 to page 9, line 2, where Applicants teach that targeted RNA or DNA, or cells containing it are contacted with oligonucleotide or analogs thereof which are configured to bind to the RNA or DNA in a manner to inhibit the expression of angiogenin whether by interfering with gene transcription as in an antigene strategy or by interfering with translation of mRNA as in an antisense strategy.

Support for claim 3 can be found at page 22, lines 5-8 of the specification, which teaches that oligonucleotide analogs refer to compounds having a modified internucleotide linkage, a modified purine or pyrimidine moiety, a modified sugar moiety, a modified 5' hydroxyl moiety, a modified 3' hydroxyl moiety or a modified 2' hydroxyl moiety.

Support for claim 4 can be found at page 22, lines 8-18 of the specification, where Applicants teach that analogs which have non-naturally occurring portions wherein one or more purine or pyrimidine moieties, sugar moieties or internucleotide phosphate linkages is chemically modified, for example, can improve stability and/or lipid solubility to enhance the ability of the oligonucleotides to penetrate into the region of cells where the RNA whose activity is to be

modulated is located. Applicants teach that it is known in the art that enhanced lipid solubility and/or resistance to nuclease digestion results by substituting a methyl group or sulfur atom for a phosphate oxygen in the internucleotide phosphodiester linkage.

Support for claim 5 can be found at page 22, line 17 to page 23 line 16 and page 26, line 19 to page 27, line 22 of the specification, where Applicants teach the use of phosphorothioate and other sulfur containing species which are known for use in the art, and that phosphorothioates are compounds in which one of the non-bridging oxygen atoms in the phosphate portion of the nucleotide is replaced by sulfur. Applicants teach the use of other modified oligonucleotides or analogs such as alkyl phosphorothioate, phosphodiester, phosphotriester, N-alkyl phosphoramidates, phosphorodithioates, alkyl phosphonates, and short chain alkyl or cycloalkyl structures may also be useful. Applicants further teach one or more phosphodiester bonds which are substituted with structures which are, at once, substantially non-ionic and non-chiral to produce mixed linkage oligonucleotides. Applicants also teach that oligonucleotide analogs may also comprise altered base or sugar units, have charged or uncharged backbones, have additions at the ends of the oligonucleotide molecule or other modifications consistent with the spirit of this invention. Applicants further teach analogs which differ from native DNA in that some or all of the phosphates in the nucleotides are replaced by phosphorothioates, methylphosphonates or other C_{1-4} alkylphosphonates such as ethyl, propyl, butyl, methyl phosphonate analogs, phosphonate modified oligodeoxynucleotides, phosphodiesters, and phosphotriesters, agents such as 2'-methylribonucleotides and chimeric oligonucleotides that are composite RNA-DNA analogues, phosphorothioates such as CH_2-NH-O-CH_2, CH_2-N(CH_3)-O-CH_2 , CH_3-O-N(CH_3)-CH_2 , CH_2-N(CH_3)-N(CH_3)-CH_2 and O-N(CH_3)-CH_2-CH_2 backbones (where phosphodiester is O-P-O-CH_2), oligonucleotides having morpholino

backbone structures, protein-nucleic acid or peptide-nucleic acid (PNA) backbones, oligonucleotides where the phosphodiester backbone of the oligonucleotide is replaced with a polyamide backbone, the bases being bound directly or indirectly to the aza nitrogen atoms of the polyamide backbone.

Support for claim 6 can be found at page 29, lines 10-11 of the specification, where Applicants teach that oligonucleotides may include at least one modified base form or "universal base" such as inosine.

Support for claim 7 can be found at page 29, lines 8-11 of the specification, where Applicants teach that oligonucleotides may have sugar mimetics, and at page 27, lines 10-13, where Applicants teach that oligonucleotides may contain cycloalkyl intersugar linkages.

Support for claim 8 can be found at page 28, lines 1-18 of the specification, where Applicants teach that the compounds may be modified by replacing one or both of the free hydroxy groups with C_{1-4} alkoxy groups (in the case of R_1 being C_{1-4} alkoxy), substituted at the 3' and/or 5' ends by R_1 being a "substituted acridine" which means any acridine derivative capable of intercalating nucleotide strands such as DNA, substituted acridines such as 2-methoxy-6-chloro-9-pentylaminoacridine, N-(6-chloro-2-methoxyacridinyl)-O-methoxydisopropylaminophosphinyl-3-aminopropanol and N-(6 chloro-2-methoxyacridinyl)-O-methoxydisopropylaminophosphinyl-5-aminopentanol, other suitable acridine derivatives which are readily apparent to persons skilled in the art, and ribozyme sequences inserted into the nucleotide sequence.

Support for claim 9 be found at page 28, line 19 to page 29, line 8 of the specification, where Applicants teach that 2' substituents include OH, SH, SCH_2, OCH_3, F, OCN, OCH_6CH_3, OCH_3OCH_3, $OCH_3O(CH_2)_n\ CH_3$, $O(CH_2)_nNH_2$ or $O\ (CH_2)_nCH_3$ where n is from 1 to about 10;

C_1 to C_{10} lower alkyl, substituted lower alkyl, alkaryl or aralkyl; Cl; Br; CN; CF_3; OCF_3; O, S, or N-alkyl; O, S, or N-alkenyl; $SOCH_3$; SO_2CH_3; ONO_2; NO_2; N_3; NH_2; heterocycloalkyl or alkaryl; aminoalkylamino; polyalkylamino; substituted silyl; an RNA cleaving group; a cholesteryl group; a conjugate; a reporter group; an intercalator; a group for improving the pharmacokinetic properties of an oligonucleotide; or a group for improving the pharmacodynamic properties of an oligonucleotide and other substituents having similar properties.

Support for claim 11 can be found in the specification at page 8, lines 13-19 and page 30, line 20 to page 35, line 10, where Applicants teach pharmaceutical compositions comprising oligonucleotides or analogs thereof having a base sequence complementary to target different sections of the nucleic acid sequence of angiogenin.

Support for claim 13 can be found in the specification at page 24, line 6 to page 29, line 11, where Applicants teach the claimed formula, that X is O, S, or C_{1-4} alkyl; B is adenine, guanine, cytosine, or thymine selected such that the oligonucleotide has a complimentary base sequence with a portion of the nucleic acid strand coding for angiogenin thereby inhibiting expression thereof; R_1 is H, C_{1-4} alkyl or substituted acridine; R_2 is H, OH, SH, F, OCH_3, OCN, or OCH_6CH_3; and n is 5 to 100. Applicants discuss additional R_1 and R_2 substituents *supra*.

Therefore, because rejected claims 1-9, 11, and 13 are the originally filed claims, and because each of the claims is supported by identical or nearly identical language in the specification as filed, the application as filed provides adequate written description under 35 U.S.C. § 112, first paragraph for claims 1-9, 11, and 13. Accordingly, the Examiner is respectfully requested to reconsider and withdraw this rejection.

In addition, applicants respectfully submit that an adequate written description of the claimed subject matter has been provided sufficient to demonstrate that applicants had possession of the claimed invention. Applicants are claiming compounds that inhibit the expression of angiogenin. The compounds have a base sequence complementary to a target portion of a nucleic acid encoding angiogenin. Applicants provide the nucleic acid encoding angiogenin. Applicants also teach base complementarity. Based on this information, one of skill in the art will be able to readily envision compounds having a base sequence complementary to a target portion of a nucleic acid encoding angiogenin and a list of such compounds is unnecessary. According to the written description guidelines, the Examiner should evaluate each claim to determine if sufficient structures, acts or functions are recited to make clear the scope and meaning of the claim. Applicants respectfully submit that they have provided sufficient structure (the entire cDNA), acts (the complementarity) and function (inhibition of expression of angiogenin) so as to meet the written description requirement. Applicants are not claiming all compounds complementary to the nucleic acid encoding angiogenin, only those that inhibit the expression of angiogenin.

II. Claims 2-9 and 13-14 Are Definite

At page 9, paragraph 11 of the instant Office Action, claims 2-9 and 13-14 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

The Examiner is of the opinion that in claim 2, the term "configured" is vague and indefinite. In response, Applicants have amended claim 2 to recite that the base sequence binds to the target.

The Examiner asserts that claim 3 appears to recite a Markush group without the proper use of Markush format. In response, Applicants have amended claim 3 to use the proper Markush group format.

The Examiner asserts that the term "improved" in claim 4 is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of skill would not be reasonably appraised of the scope of the invention. In response, Applicants have amended claim 4 to recite that the compound is improved as compared to an unmodified compound.

The Examiner asserts that claim 5 appears to recite a Markush group without the proper use of Markush format. The Examiner also asserts that this claim recites a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation, which is considered indefinite. In response, Applicants have amended claim 5 to use the proper Markush group format. In addition, Applicants have amended claim 5 to remove the narrow range. The narrow range is presently recited in new claim 22. Applicants respectfully submit that this amendment is made as to form only since the deleted limitation has been presented in a new claim.

The Examiner asserts that claims 8, 13, and 14 recite a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation. In response, Applicants have amended claims 8 and 13 to remove the narrow ranges. The narrow ranges are presently recited in new claims 23 and 24. Applicants respectfully submit that these amendments are made as to form only since the deleted limitations have been presented in a new claim. With respect to claim 14, Applicants respectfully submit that claim 14 does not recite a broad range or

limitation together with a narrow range or limitation that falls within the broad range or limitation.

The Examiner asserts that the term "improving" in claims 9, 13, and 14 is a relative term that renders the claim indefinite. The Examiner further asserts that these claims appear to recite a Markush group without the proper use of Markush format. In response, Applicants have amended claims 9 and 13 to use the proper Markush group format. In addition, Applicants have amended claims 9 and 13 to recite that the compound or oligonucleotide is improved as compared to an unmodified compound or oligonucleotide. With respect to claim 14, Applicants respectfully submit that claim 14 recites proper Markush group language and does not recite the language "improving."

In view of the above, Applicants respectfully request withdrawal of the rejections of amended claims 2-5, 8, 9, and 13 and claims 6, 7, and 14 under 35 U.S.C. § 112, second paragraph.

III. Rejections of Claim 21 Under 35 U.S.C. § 102(b) Over Vallee et al. and Under Obviousness-Type Double Patenting

At page 4, paragraph 5, claim 21 stands rejected under 35 U.S.C. § 102(b), as being anticipated by Vallee et al., U.S. Patent No. 4,916,073. The Examiner is of the opinion that Vallee et al. discloses a method for detecting the presence of angiogenin in a sample with a labeled oligonucleotide comprising a base sequence complementary to a target portion of a nucleic acid encoding angiogenin.

At page 9, paragraph 10, claim 21 stands rejected under the judicially created doctrine of obviousness-type double patenting. The Examiner is of the opinion that pending claim 21 is not patentably distinct from claim 7 of U.S. Patent No. 6,265,388 because claim 7 recites a method

for detecting the presence of angiogenin in a sample comprising contacting the sample with a labeled oligonucleotide or analog that is complementary to a nucleic acid encoding angiogenin.

Applicants respectfully traverse these rejections. However, without acquiescing to the rejections, Applicants have cancelled claim 21 without prejudice to the filing of any appropriate continuation application, thereby rendering the rejections moot.

IV. Claims 1-9, 11, and 13 are Non-Obvious Over Vallee et al. in View of Olson et al., Milligan et al., Burch, Anderson et al., and Artavanis-Tsakonas et al.

At page 5, paragraph 8 of the present Office Action, claims 1-9, 11, and 13 stand rejected under 35 U.S.C. § 103(a), as being obvious over Vallee et al., U.S. Patent No. 4,916,073, in view of Olson et al., *Cancer Research* (1994) 54:4576, Milligan et al., *J. Med. Chem.* (1993) 36:1923, Burch, U.S. Patent No. 5,135,917, Anderson et al., U.S. Patent No. 5,442,049, and Artavanis-Tsakonas et al., U.S. Patent No. 5,637,471. The Examiner is of the opinion that one of ordinary skill in the art would have been motivated to make and use antisense oligonucleotides that targeted angiogenin in order to inhibit angiogenin expression because Olson et al. teaches that inhibition of angiogenesis is an attractive therapeutic target for the treatment of both primary and metastatic cancer because angiogenesis is crucial in growth and spread of metastatic cancer. The Examiner further asserts that one of ordinary skill in the art would have been motivated to make antisense oligonucleotides that targeted angiogenin gene expression, because Milligan et al. teaches that antisense oligonucleotides can be used to specifically inhibit expression of a particular gene and because Vallee et al. discloses the mRNA sequence of human angiogenin. The Examiner also asserts that one of skill would have been motivated to make compositions comprising antisense oligonucleotides with various modifications, as taught by Milligan et al., the Burch reference, Anderson et al., and Artavanis-Tsakonas et al. because the aforementioned

prior art teaches that modifications to the antisense oligonucleotides enhances stability to nucleases, increases affinity of the oligonucleotides for their targets, and improves cellular uptake and permeability. The Examiner concludes that, absent evidence to the contrary, one of ordinary skill in the art would have had reasonable expectation of success in modifying oligonucleotides because making and using such modifications were well known in the prior art. Applicants respectfully traverse the Examiner's rejection.

Applicants' claims are directed to compounds and compositions for inhibiting expression of angiogenin comprising an oligonucleotide or analog thereof having a base sequence complementary to a target portion of a nucleic acid encoding angiogenin.

Applicants respectfully submit that based on the teachings of Vallee et al., Olson et al., Milligan et al., Burch, Anderson et al., and Artavanis-Tsakonas et al. as a whole, one of skill in the art would not have been motivated to modify Vallee et al. to produce Applicants' claimed subject matter with a reasonable expectation of success.

Applicants respectfully submit that the general teachings of Milligan et al. and the cDNA sequence of angiogenin taught by Vallee et al., do not provide one of skill in the art with a reasonable expectation of success of making Applicants' compounds. The use of antisense molecules to inhibit the expression of a gene product is very unpredictable. In fact, the Milligan et al. reference cited by the Examiner states that antisense oligonucleotides can be designed to target any gene within the genome **in principle** (page 1923, left column). Thus, this reference teaches that the ability to target any and all genes is theoretical. This reference describes **significant hurdles which have limited progress** in the development of antisense oligonucleotides as therapeutic agents (page 1923, left column).

Furthermore, one of skill in the art would not be motivated by the references cited by the Examiner to arrive at Applicants' invention. The Vallee et al. reference teaches the sequence of a cDNA of the angiogenin gene. The Examiner recognizes that Vallee et al. does not disclose an oligonucleotide or analog thereof having a base sequence complementary to a target portion of a nucleic acid encoding angiogenin, for inhibiting expression of angiogenin. Additionally, nowhere does Vallee et al. teach or suggest any antisense approach to inhibiting the expression of angiogenin.

Olson et al. fails to cure the deficiencies of Vallee et al. Olson et al. teaches the direct inhibition of the angiogenin protein based upon inhibitors which bind to the protein, as distinguished from the inhibition of gene expression of angiogenin. Olson et al. therefore teach inhibition of mature, functional cellular angiogenin protein and do not teach or suggest inhibition of the cellular production of angiogenin by the use of an antisense molecule. Olson et al. simply does not provide motivation to look to an antisense approach.

Similarly, Milligan et al., Burch, Artavanis-Tsakonas et al. and Anderson et al. fail to cure the deficiencies of Vallee et al. or Olson et al. The Milligan et al. reference teaches generally that an oligonucleotide can be designed to target any gene whose sequence is known. Milligan et al. is not at all concerned with angiogenin, antisense approaches to inhibiting the expression of angiogenin or the claimed compounds. Burch, Artavanis-Tsakonas and Anderson et al. are each directed to modifications and are not directed to angiogenin, antisense approaches to inhibiting the expression of angiogenin or the claimed compounds.

Based on the above, Applicant respectfully requests that the Examiner reconsider and withdraw the rejections of claims 1-9, 11, and 13 under 35 U.S.C. § 103(a) over Vallee et al., in view of Olson et al., Milligan et al., Burch, Anderson et al., and Artavanis-Tsakonas et al.

V. Conclusion

Applicants respectfully request entry and consideration of the foregoing amendments and reconsideration and allowance of the case. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is requested to telephone the undersigned at the number below.

Respectfully submitted,

Dated: June 12, 2002

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Version of Amendments with Markings to Show Changes Made

In the Specification:

At page one of the specification, please replace the first sentence with the following sentence:

--This application is a continuation of U.S. Patent Application Serial No. 09/045,301, filed on March 20, 1998, now U.S. Patent No. 6,265,388, issued on July 24, 2001.--

In the Claims:

Kindly amend the claims as follows:

2. (Amended) The compound of claim 1 wherein the base sequence [is configured to bind] binds to the target portion of the nucleic acid in a manner to inhibit the expression of angiogenin.

3. (Amended) The compound of claim 2 wherein the oligonucleotide analog comprises a modification selected from the group consisting of a modified internucleotide linkage, a modified purine or pyrimidine moiety, a modified sugar moiety, a modified 5' hydroxyl moiety, a modified 3' hydroxyl moiety [or] and a modified 2' hydroxyl moiety.

4. (Amended) The compound of claim 3 wherein the modified internucleotide linkage comprises a substituent having an improved aqueous or lipid solubility or improved resistance to nuclease digestion as compared to an unmodified compound.

5 (Amended) The compound of claim 4 wherein the modified internucleotide linkage is selected from the group consisting of phosphorothioate, [alkyl or cycloalkyl phosphorothioate,] N-alkyl phosphoramidates, [or] cycloalkyl phosphoramidates, [phosphorodithioates,] alkyl phosphonates, [or] cycloalkyl phosphonates, phosphodiester, phosphotriester, C_1 - C_4 alkyl, cycloalkyl, short chain heteroatomic backbone, [or] short chain heterocyclic backbone, morpholino backbone, polyprotein-nucleic acid backbone, [or] peptide-nucleic acid backbone, polyamide, CH_2-NH-O-CH_2, CH_2-N(CH_3)-O-CH_2 , CH_3-O-N(CH_3)-CH_2 , CH_2-N(CH_3)-N(CH_3)-CH_2, and O-N(CH_3)-CH_2-CH_2.

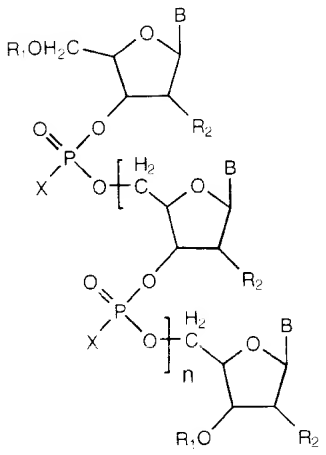
8. (Amended) The compound of claim 3 wherein the modified 5' or 3' hydroxyl moiety is selected from the group consisting of C_{1-4} alkoxy, intercalating agent, peptide, enzyme, and ribozyme[, substituted acridine, 2-methoxy-6-chloro-9-pentylaminoacridine, N-(6-chloro-2-methoxyacridinyl)-O-methoxydisopropylaminophosphinyl-3-aminopropanol and N-(6 chloro-2-methoxyacridinyl)-O-methoxydisopropylaminophosphinyl-5-aminopentanol].

9. (Amended) The compound of claim 3 wherein the modified 2' hydroxyl moiety is selected from the group consisting of OH, SH, SCH_2, OCH_3, F, OCN, OCH_6CH_3, OCH_3OCH_3, $OCH_3O(CH_2)_n$ CH_3, $O(CH_2)_nNH_2$, [or] O $(CH_2)_nCH_3$, where n is from 1 to about 10; C_1 to C_{10} lower alkyl, substituted lower alkyl, substituted lower alkaryl [or] substituted lower aralkyl; Cl; Br; CN; CF_3; OCF_3; O, S, [or] N-alkyl; O, S, [or] N-alkenyl; $SOCH_3$; SO_2CH_3; ONO_2; NO_2; N_3; NH_2; heterocycloalkyl, [or] alkaryl; aminoalkylamino; polyalkylamino; substituted silyl; an RNA cleaving group; a cholesteryl group; a conjugate; a reporter group; an intercalator; a group for improving the pharmacokinetic properties of an oligonucleotide as compared to an unmodified

compound; and a group for improving the pharmacodynamic properties of an oligonucleotide as compared to an unmodified compound.

13. (Amended) A compound for inhibiting expression of angiogenin having the formula:

5'



3'

wherein

X is selected from the group consisting of O, S, [or] and C_{1-4} alkyl;

B is selected from the group consisting of adenine, guanine, cytosine, [or] and thymine, selected such that the oligonucleotide has a complementary base sequence with a portion of a target nucleic acid strand coding for angiogenin thereby inhibiting expression thereof;

R_1 is selected from the group consisting of H, C_{1-4} alkyl, intercalating agent, peptide, enzyme, and ribozyme[, substituted acridine, 2-methoxy-6-chloro-9-pentylaminoacridine, N-(6-chloro-2-methoxyacridinyl)-O-methoxydiisopropylaminophosphinyl-3-aminopropanol and N-(6 chloro-2-methoxyacridinyl)-O-methoxydiisopropylaminophosphinyl-5-aminopentanol];

R_2 is selected from the group consisting of H, OH, SH, SCH_2, OCH_3, F, OCN, OCH_6CH_3, OCH_3OCH_3, [$OCH_3O(CH_2)_n$ CH_3, $O(CH_2)_nNH_2$, or O $(CH_2)_nCH_3$, where n] $OCH_3O(CH_2)_p$ CH_3, $O(CH_2)_pNH_2$, O $(CH_2)_pCH_3$, where p is from 1 to about 10; C_1 to C_{10} lower

alkyl, substituted lower alkyl, substituted lower alkaryl, [or] substituted lower aralkyl; Cl; Br; CN; CF_3; OCF_3; O, S, [or] N-alkyl; O, S, [or] N-alkenyl; $SOCH_3$; SO_2CH_3; ONO_2; NO_2; N_3; NH_2; heterocycloalkyl, [or] alkaryl; aminoalkylamino; polyalkylamino; substituted silyl[;]; an RNA cleaving group; a cholesteryl group; a conjugate; a reporter group; an intercalator; a group for improving the pharmacokinetic properties of an oligonucleotide as compared to an unmodified oligonucleotide; [or] and a group for improving the pharmacodynamic properties of an oligonucleotide as compared to an unmodified oligonucleotide; and

n is 5 to 100.